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Breast cancers with rare histologies

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INTRODUCTION

Most invasive breast malignancies are epithelial in origin and categorized as invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC). IDCs account for approximately 70 to 80 percent of invasive breast cancer diagnoses, characterized microscopically by cords and nests of tumor cells with variable amounts of gland formation. ILCs, which account for approximately 5 to 10 percent of invasive breast cancer diagnoses, are characterized microscopically by small cells often in a single file pattern. Treatment paradigms for IDC and ILC are identical, and largely determined by estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status on the tumor cells.

Aside from IDC and ILC, several rarer histologic subtypes account for the remaining invasive breast cancers. These histologies include: tubular carcinoma, mucinous carcinoma, medullary carcinoma, micropapillary carcinoma, metaplastic carcinoma, neuroendocrine carcinoma, and adenoid cystic carcinoma. This topic will review these rare breast cancer subtypes with regards to clinical presentation, pathologic features, and disease management recommendations.

Other issues, including a deeper discussion on the pathology of breast cancer and management of early and metastatic breast cancer are discussed elsewhere.

- (See "[Pathology of breast cancer](#)".)
- (See "[Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer](#)".)
- (See "[Overview of the approach to metastatic breast cancer](#)".)

CLINICAL PRESENTATION

Like most invasive ductal carcinomas (IDCs) or invasive lobular carcinomas, breast cancers with rare histologies are often identified clinically by screening mammography or by the patient or their care provider noting a palpable abnormality in the breast on physical examination. (See ["Clinical features, diagnosis, and staging of newly diagnosed breast cancer"](#).)

In regards to clinical presentation and breast imaging findings, most rare breast cancer subtypes are challenging to distinguish from IDC; however, there are a few clinical and radiographic features to note:

- Pure mucinous carcinomas and medullary carcinomas generally appear as round or oval well circumscribed masses on mammography. Sonographically, mucinous carcinomas may be isoechoic due to subcutaneous fat [1], and medullary carcinomas may mimic the appearance of fibroadenomas [2]. These benign characteristics on breast imaging can potentially lead to delay in diagnosis [3].
- Medullary carcinomas occur more frequently in younger patients and they are also reported to be more frequent in individuals with a pathogenic germline variant in breast cancer susceptibility genes 1 (*BRCA1*) [4]. They are more likely to be hormone receptor-negative and human epidermal growth factor receptor 2-negative (triple-negative).
- Metaplastic carcinomas are often reported as being rapidly enlarging masses, which is consistent with their highly aggressive nature. On sonography, solid and cystic components may be noted due to central tumor necrosis given the very rapid growth of the lesion [5].

DIAGNOSIS

Pathologic considerations — The pathology of breast cancer, including breast cancers with rare histologies, is reviewed elsewhere. (See ["Pathology of breast cancer"](#).)

It is important to note that complete excision and examination of the tissue by an experienced pathologist is necessary to classify a tumor as belonging to one of these rare breast cancer histologies. A final pathologic diagnosis should not be made based on needle biopsy alone.

Furthermore, IDC may be classified as having features consistent with one of these rare histologies, such as IDC with tubular or mucinous features. If the dominant histology is IDC, it does not belong to one of these rare breast cancer histologies and should be treated as an IDC.

The descriptions below focus on tumors that are purely composed of these rare histologic subtypes.

PROGNOSIS AND MANAGEMENT

Hormone receptor-positive, HER2-negative, good prognosis subtypes

Tubular and mucinous (colloid) breast carcinomas — Pure tubular and mucinous (colloid) breast carcinomas generally have an excellent prognosis [6-10]. When compared with grade 1 invasive ductal carcinoma (IDC), they have lower incidence of lymph node metastases or lymph vascular invasion at diagnosis.

In a study comparing the clinical outcomes of 102 patients with pure tubular carcinoma to 212 patients with grade 1 IDC, tubular carcinoma histology was associated with longer disease-free and breast cancer specific survival [11].

- **Surgery** – Surgical management of pure tubular carcinomas and mucinous carcinomas is identical to surgical management recommendations for individuals with more common breast cancer histologies. (See "[Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer](#)".)
- **Adjuvant therapy**
 - **Endocrine therapy** – Because prospective data are limited for mucinous and tubular/cribriform histologies, our approach towards endocrine therapy for these entities is generally the same as for more common histologies, although we typically suggest a five-year course of treatment rather than extended durations given their overall excellent prognosis. (See "[Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer](#)" and "[Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer](#)".)

However, patients with mucinous or tubular/cribriform histotypes have a better prognosis and therefore may derive a smaller absolute recurrence risk reduction from endocrine therapy compared with patients with other breast cancer histologies (although they would still experience a similar chemoprotective effect against a second breast cancer). As such, some patients, particularly those with smaller (<3 cm), node-negative tumors [12], or those with comorbidities that increase the risks of treatment (eg, osteoporosis), may reasonably choose not to take adjuvant endocrine therapy.

- **Chemotherapy** – Due to the excellent prognosis of pure tubular and mucinous carcinomas, which are frequently hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative, use of chemotherapy or gene expression profiling such as Oncotype Dx Recurrence Score is not recommended, as there would be no anticipated benefit from use of adjuvant chemotherapy treatment.
- **Radiation** – For those who undergo breast conservation, administration of adjuvant radiation therapy to decrease likelihood of local recurrence should also be considered. Our approach toward adjuvant radiation therapy and threshold for recommending radiation treatment is similar to the approach utilized for more common breast cancer histologies. (See ["Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer"](#).)

Hormone receptor-negative, HER2-negative, good prognosis subtypes

Medullary carcinoma — Surgical management of medullary carcinoma is identical to management recommendations for those with IDC and similarly, adjuvant radiation therapy is recommended for those who undergo breast conservation or have positive axillary lymph nodes. (Neo)adjuvant systemic therapy recommendations are also identical to those for triple-negative IDC and are described elsewhere. (See ["ER/PR negative, HER2-negative \(triple-negative\) breast cancer"](#).)

Despite being high grade and more likely triple-negative, medullary breast carcinomas also have lower incidence of axillary lymph node involvement at presentation and superior prognosis compared with high grade, triple-negative IDC [13,14].

For example, in a retrospective study of 46 patients with medullary histology compared with 1444 control subjects with infiltrating ductal carcinoma, 10-year distant relapse-free survival was superior for those with medullary carcinoma (95 versus 78 percent) [13]. A similar retrospective study noted that 14-year distant relapse-free survival for 127 patients with medullary carcinoma was 76 compared with 64 percent for IDCs (n = 8096) of similar stage, age at diagnosis, and hormone receptor status [14].

Adenoid cystic carcinoma — For adenoid cystic carcinoma, we suggest surgical excision alone; most do not need adjuvant treatment.

Most adenoid cystic carcinomas are low grade and triple-negative by histology. In contrast to other triple-negative breast carcinomas, adenoid cystic carcinomas of the breast generally have a very favorable prognosis, with complete surgical excision alone being curative in most circumstances in early-stage disease [15,16].

For example, in a study utilizing the Surveillance, Epidemiology, and End Results (SEER) Program, 338 with adenoid cystic carcinoma of the breast diagnosed between 1977 to 2006 had five-year, 10-year, and 15-year relative survival of 98, 95, and 91 percent, respectively [16].

In general, there is a low rate of axillary lymph node metastases; therefore, sentinel lymph node excision may not be necessary. If a patient undergoes breast conservation, adjuvant radiation therapy is generally recommended in accordance with the treatment paradigm for other breast malignancies.

In terms of systemic therapies, adenoid cystic carcinomas are generally not chemotherapy sensitive; therefore, adjuvant chemotherapy is not recommended. As most adenoid cystic breast cancers are hormone receptor-negative and HER2-negative, there is also rarely a role for adjuvant hormonal therapy or HER2 directed therapy. At present, there are no approved systemic therapies for metastatic adenoid cystic carcinoma, including those that originate in the salivary gland and breast. For patients with metastatic adenoid cystic carcinoma, we recommend consideration of clinical trial enrollment. (See "[Malignant salivary gland tumors: Treatment of recurrent and metastatic disease](#)".)

Poor prognosis subtypes

Micropapillary carcinoma — Micropapillary carcinoma of the breast is generally considered to have a less favorable prognosis due to the fact that tumors have a proclivity for lymph node metastases even when the primary tumor is small in size [17]. Micropapillary carcinomas have been reported to be hormone receptor positive or negative and HER2 positive or negative. Surgical, radiation, and systemic therapy recommendations are identical to those for IDCs [18].

In terms of surgical approach, a study of 1203 patients diagnosed with early-stage invasive micropapillary carcinoma from the SEER database indicated that breast conservation was at least equivalent to mastectomy in terms of long-term survival outcomes [18].

Although data are very limited, there are some series that have suggested that prognosis for early-stage micropapillary carcinomas of the breast are similar to IDCs of identical stage and receptor status [19]. For example, a retrospective study that examined prognostic differences between invasive micropapillary carcinoma (327 cases) and IDC (4979 cases) matched for age, tumor size, nodal status, hormone receptor status, and HER2 status, patients with micropapillary carcinoma had no significantly reduced overall survival or disease-free survival compared with patients with IDC [19].

Neuroendocrine carcinoma — Neuroendocrine carcinoma of the breast is also considered to have a less favorable prognosis compared with IDC, as tumors are more likely to be larger,

higher grade, and triple-negative, although hormone receptor-positive, HER2-negative neuroendocrine carcinoma is also observed [20]. As above, we use the same surgical, radiation, and systemic therapy treatment paradigms for neuroendocrine carcinomas that are used for IDCs and based on estrogen receptor, progesterone receptor, and HER2 status.

Although there have been case reports of administering systemic therapy regimens such as the combination of [cisplatin](#) and [etoposide](#) [21] to individuals with early-stage pure small cell carcinoma of the breast, the benefit of platinum-based chemotherapy regimens versus standard anthracycline and taxane-based regimens used more commonly in breast cancer is unknown given the paucity of data available [22]. As such, we favor standard breast cancer treatment regimens.

Metaplastic carcinoma — Metaplastic carcinomas are more likely to be triple-negative and generally have inferior prognosis compared with triple-negative IDC [23].

Early-stage disease — For patients with early-stage metaplastic carcinomas, surgical and radiation treatment recommendations for localized metaplastic carcinomas are identical to those for IDCs. For most patients, we also administer systemic therapy according to the same treatment algorithms as for those with IDCs. For example, for most patients with stage II to III disease, neoadjuvant chemotherapy with [pembrolizumab](#) is offered, followed by surgery and sometimes radiation; while those with earlier stage disease are typically treated initially with surgery followed by adjuvant chemotherapy and sometimes radiation. However, others have argued against the use of systemic therapy in metaplastic tumors, given their relative chemotherapy insensitivity [24,25].

While we offer most systemic therapy for most metaplastic tumors, rarely, metaplastic carcinomas are low grade and predominantly adenosquamous histology. These low grade, adenosquamous tumors generally have good prognosis without (neo)adjuvant systemic therapies and we suggest against use of systemic therapy in this subset.

With regards to systemic therapy, it has been noted in the limited studies available that those patients with localized metaplastic carcinoma treated with neoadjuvant chemotherapy often have poor response to chemotherapy, indicating that many of these tumors may be chemotherapy-refractory [26]. As an example, in a single institution study in 18 patients with metaplastic breast cancer treated with neoadjuvant chemotherapy, 28 percent progressed on initial treatment, and the overall pathologic complete response (pCR) rate was just 11 percent, which is lower than expected in patients with triple-negative breast cancer. In separate trials, the pCR rate in patients with triple-negative breast cancer from more typical histologies often

exceeds 50 percent. (See ["Choice of neoadjuvant chemotherapy for HER2-negative breast cancer"](#), section on 'Special considerations for triple-negative disease'.)

Nevertheless, subsequent studies have suggested that some metaplastic carcinomas do indeed benefit from systemic therapy, with rates of pCR at surgery of approximately 20 percent using conventional [doxorubicin](#) and [cyclophosphamide](#) followed by [paclitaxel](#) with or without [carboplatin](#) chemotherapy [27].

There is enthusiasm for utilizing neoadjuvant chemoimmunotherapy in the early-stage treatment setting for this tumor type, as [pembrolizumab](#) was also US Food and Drug Administration (FDA) approved in combination with [paclitaxel/carboplatin](#) and [adriamycin/cytosan](#) for use in stage II to III triple-negative breast cancer in July 2021 [28]. Although reports of clinical outcomes of metaplastic breast carcinomas treated with neoadjuvant chemoimmunotherapy are lacking, we do use this treatment modality for those patients with clinical stage II to III disease at presentation, with close clinical monitoring of treatment response to therapy. For those patients without apparent clinical benefit or overt progressive disease while on neoadjuvant systemic therapy, we advocate for discontinuing neoadjuvant systemic therapy and proceeding directly to surgery.

Metastatic disease — Treatment for patients with metastatic metaplastic carcinoma is with chemotherapy, with choice of therapy similar to triple-negative IDCs. (See ["ER/PR negative, HER2-negative \(triple-negative\) breast cancer"](#), section on 'Metastatic disease'.)

Additionally, for those with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of 10 or greater, we suggest the addition of the programmed cell death protein 1 (PD-1) inhibitor [pembrolizumab](#), extrapolating from the approach in more common histologies.

In November 2020, the FDA approved the use of [pembrolizumab](#) in combination with chemotherapy for metastatic triple-negative breast cancer that is positive for PD-L1 (CPS of 10 or greater) based on the results of the KEYNOTE-355 study, which demonstrated an improvement in progression-free and overall survival compared with chemotherapy alone [29]. Several reports have indicated that metaplastic breast carcinomas often express PD-L1 (approximately 46 percent of cases) [30]; therefore, may be more likely to benefit from immunotherapy-based treatments. Indeed, case reports have reported responses and durable clinical benefit observed with immunotherapy treatment in patients with metastatic metaplastic carcinoma [31,32].

Furthermore, a recently published analysis of the SWOG1609 study demonstrated that exceptional responses to the combination of cytotoxic T lymphocyte antigen 4 inhibitor [ipilimumab](#) plus PD-1 inhibitor [nivolumab](#) were observed among metastatic metaplastic breast

cancers [33]. However, pending further data, we do not use ipilimumab or nivolumab outside of a clinical trial for patients with metaplastic carcinoma.

SUMMARY AND RECOMMENDATIONS

- **Introduction** – Most invasive breast malignancies are epithelial in origin and categorized as invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC). Several rarer histologic subtypes account for the remaining invasive breast cancers. (See ['Introduction'](#) above.)

These histologies include the following:

- Tubular carcinoma
 - Mucinous carcinoma
 - Medullary carcinoma
 - Micropapillary carcinoma
 - Metaplastic carcinoma
 - Neuroendocrine carcinoma
 - Adenoid cystic carcinoma
- **Clinical presentation** – Like most IDCs or ILCs, breast cancers with rare histologies are often identified clinically by screening mammography or by the patient or their care provider noting a palpable abnormality in the breast on physical examination. However, there are a few clinical and radiographic features to note (see ['Clinical presentation'](#) above):
 - Pure mucinous carcinomas and medullary carcinomas generally appear as round or oval well circumscribed masses on mammography.
 - Medullary carcinomas occur more frequently in younger patients, and they are also reported to be more frequent in individuals with a pathogenic germline variant in breast cancer susceptibility genes 1 (*BRCA1*).
 - Metaplastic carcinomas are often reported as being rapidly enlarging masses.
 - **Hormone receptor-positive, HER2-negative, good prognosis subtypes** – These include tubular and mucinous (colloid) breast carcinomas. Although they are typically managed in a manner similar to other hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative cancers, there is no role for chemotherapy. Endocrine therapy is typically administered, as for other types of hormone receptor-positive breast cancer.

We typically suggest a five-year course rather than longer durations (**Grade 2C**); however, those who are tolerating treatment well or have risk factors (T3 tumors or node-positive disease) may elect for up to 10 years of treatment. (See '[Hormone receptor-positive, HER2-negative, good prognosis subtypes](#)' above.)

- **Hormone receptor-negative, HER2-negative, good prognosis subtypes** – Management is as follows (see '[Hormone receptor-negative, HER2-negative, good prognosis subtypes](#)' above):
 - Medullary carcinomas are managed in a similar fashion to other triple-negative breast cancers. (See '[ER/PR negative, HER2-negative \(triple-negative\) breast cancer](#)' and '[Medullary carcinoma](#)' above.)
 - For triple-negative adenoid cystic carcinoma, we suggest surgical excision alone, rather than (neo)adjuvant treatment (**Grade 2C**). (See '[Adenoid cystic carcinoma](#)' above.)
- **Poor prognosis subtypes**
 - Micropapillary carcinomas have been reported to be hormone receptor positive or negative and HER2 positive or negative. Surgical, radiation, and systemic therapy recommendations are identical to those for IDCs. (See '[Micropapillary carcinoma](#)' above.)
 - Neuroendocrine carcinoma of the breast is also considered to have a less favorable prognosis compared with IDC. We use the same surgical, radiation, and systemic therapy treatment paradigms that are used for IDCs. Although [cisplatin](#) and [etoposide](#) regimens have been described, we favor standard chemotherapy options for systemic therapy. (See '[Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer](#)' and '[ER/PR negative, HER2-negative \(triple-negative\) breast cancer](#)'.)
 - Although metaplastic carcinomas may be less chemosensitive than IDC, we use the same treatment paradigms that are used for IDCs, including chemoimmunotherapy where indicated. (See '[Metaplastic carcinoma](#)' above.)

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Contributor Disclosures

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